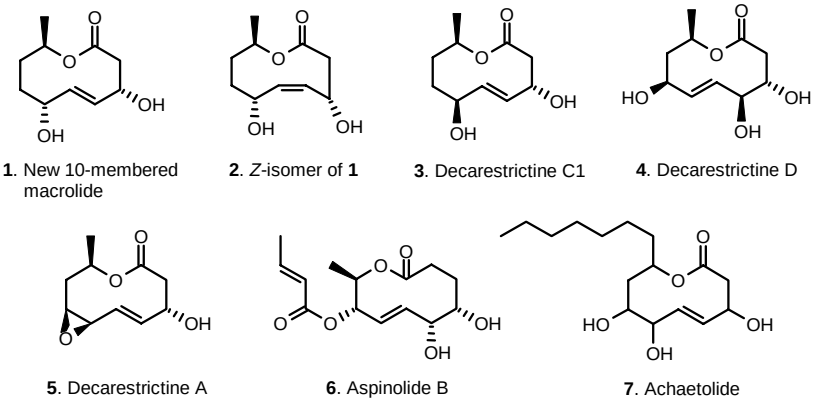
Protecting group directed ring-closing metathesis (RCM): the First total synthesis of anti-malarial nonenolide

Debendra K. Mohapatra,[a] Dhondi K. Ramesh,[a] Michael A. Giardello,[b] Mukund S. Chorghade,[a] Mukund K. Gurjar,[a] and Robert H. Grubbs[c]

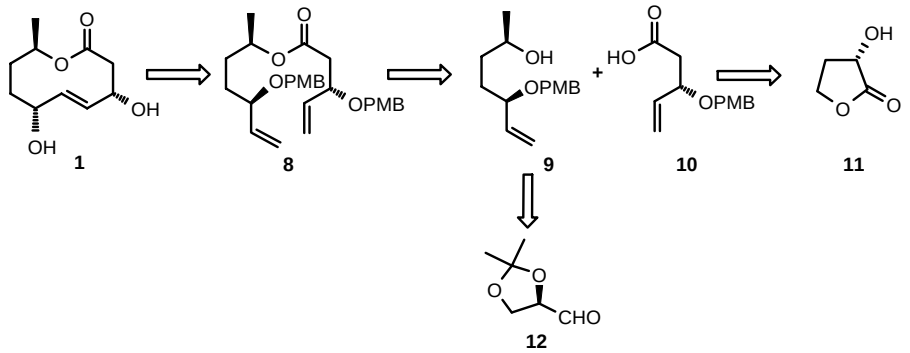
[a]Division of Organic Chemistry:Technology, National Chemical Laboratory, Pune 411 008, India; [b]Materia Inc., 60, N Gabriel Boulevard, Pasadena, 91107, USA ; [c]Arnold and Mable Beckman Laboratories of Chemical Synthesis, Division Of Chemistry and Chemical Engeneering, California Institute of Technology, Pasadena, 91125, USA

In recent years, secondary metabolites isolated from *Cordeceps militaris* have received attention due to their unique structures and specific biological activities. Cordycepins (3'-deoxyadenosine), with antifungal, antivirus, and antitumor activities, is one of selected secondary metabolites that have been previously isolated from *Cordyceps militaris*. Compound **1** was recently isolated as a white solid from *Cordyceps militaris BCC 2816*; the structure was elucidated and the stereochemistry confirmed by spectral data and X-ray crystallographic analysis.[1]



Some natural nonenolides with chiral centres on both sides of double bond

As part of our ongoing programme on the synthesis of natural lactones with ring-closing metathesis (RCM) as key step, we have devised a stereoselective synthesis of nonenolide **1.** The retrosynthetic analysis is depicted in Scheme 1. The macrolactonization step relies on a RCM on a diolefinic ester. Strategic bond disconnection in ester **8** leads to chiral, nonracemic fragments **9** and **10** that could be derived from (*S*)-α-hydroxy-γ-butyrolactone (**11**) and 1,2-*O*-isopropylidene (D)-glyceraldehyde (**12**), respectively.



Scheme 1. Retrosynthetic analysis

References

1. Rukachaisirikul, V.; Pramjit, S,; Pakawatchai, C,; Isaka, M.; Supothina, S. *J. Nat. Prod*. **2004,** *67*, 1953-1955.

Chorghade Enterprises / THINQ Pharma –CRO
Natick, MA

"Stitching and Bonding Pune and Pasadena Together: Olefin Metatheses in the Synthesis of Natural Products

Mukund S. Chorghade, Ph.D.,

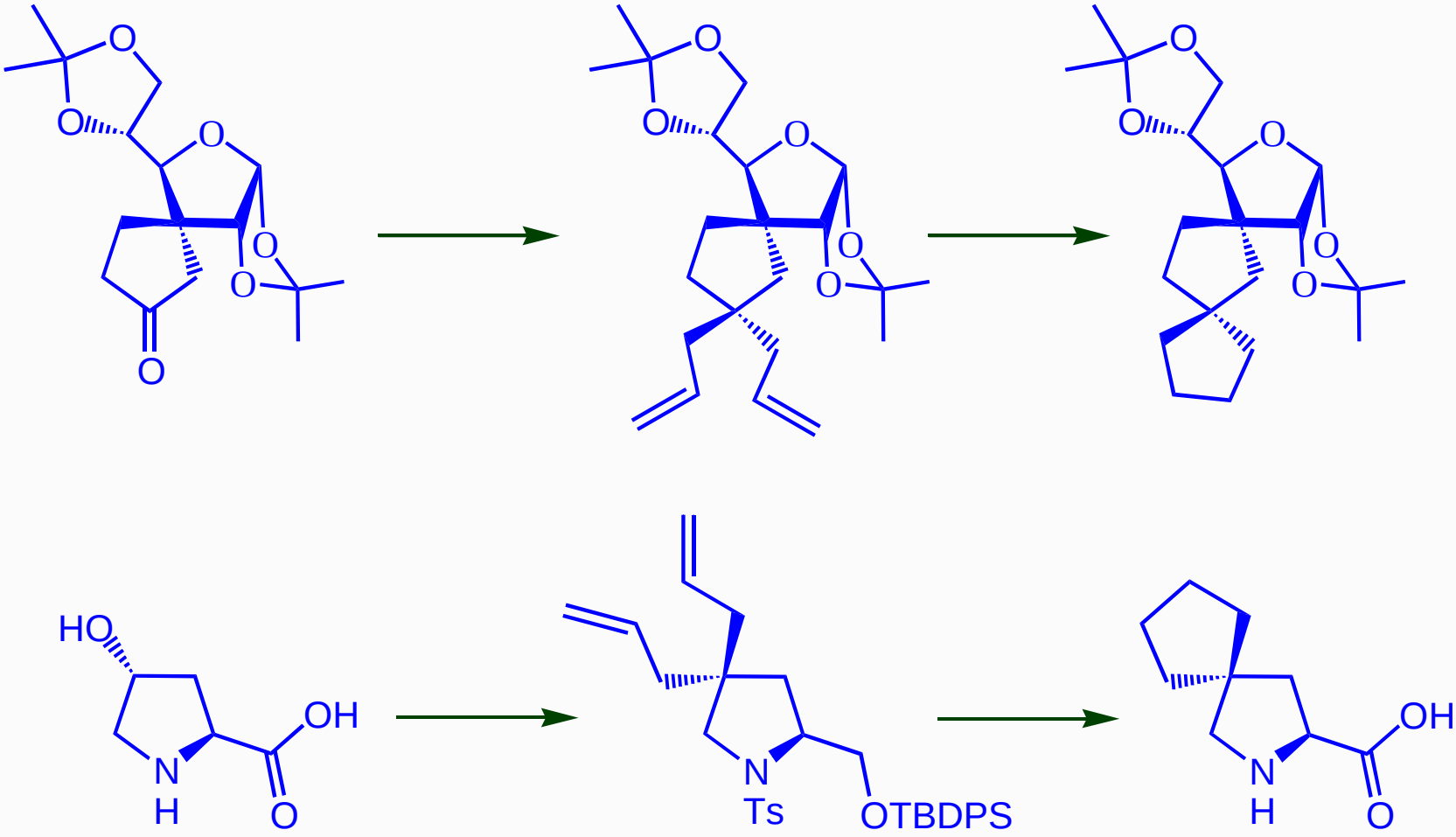
President and Chief Scientific Officer

And,

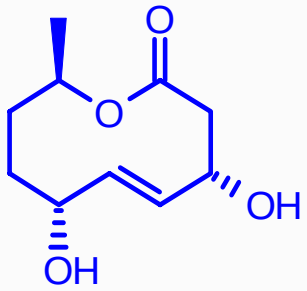
Mukund K. Gurjar, Debendra K. Mohapatra and Ramesh Dhondi

National Chemical Laboratory, Pune, India

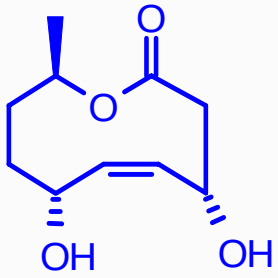
Iterative Approach



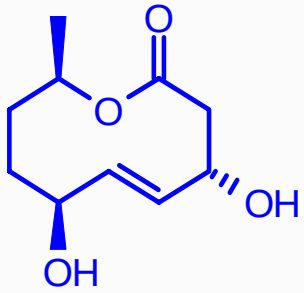
Biologically Active10-Membered Macrolides



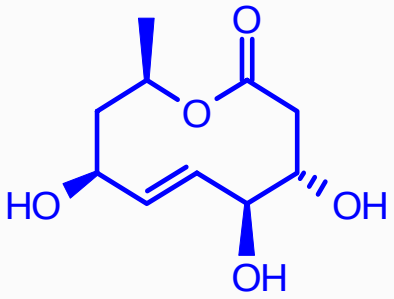
1. New 10-membered macrolide



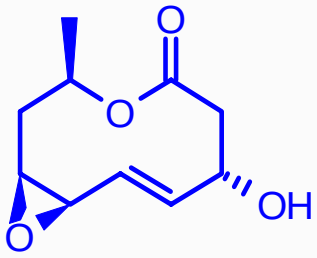
2. *Z*-isomer of **1**



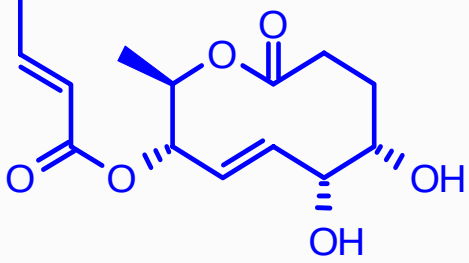
3. Decarestrictine C1



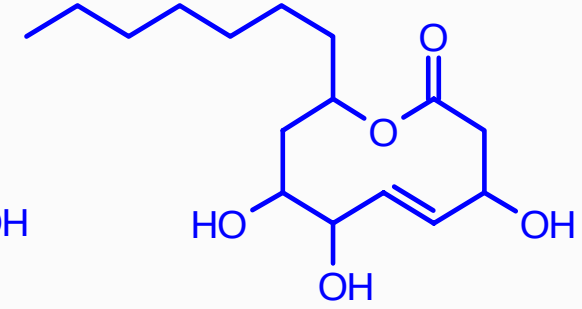
4. Decarestrictine D



5. Decarestrictine A

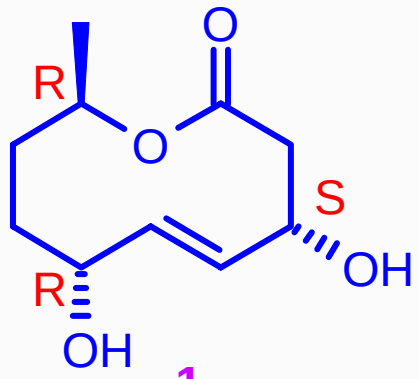


6. Aspinolide B



7. Achaetolide

New Anti-Malarial Nonenolide



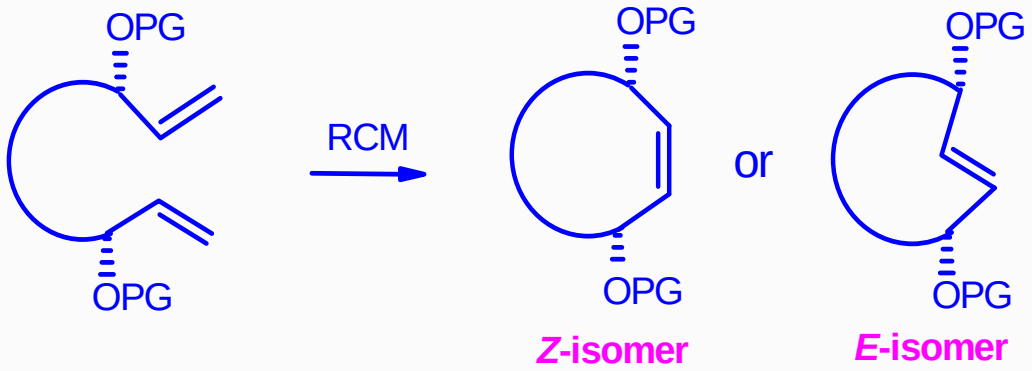
1

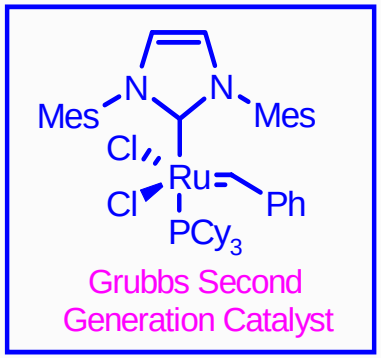
Isolation: white solid from *Cordyceps militaris BCC 2816*

Activity: antimalarial activity against *Plasmodium falciparum* K1

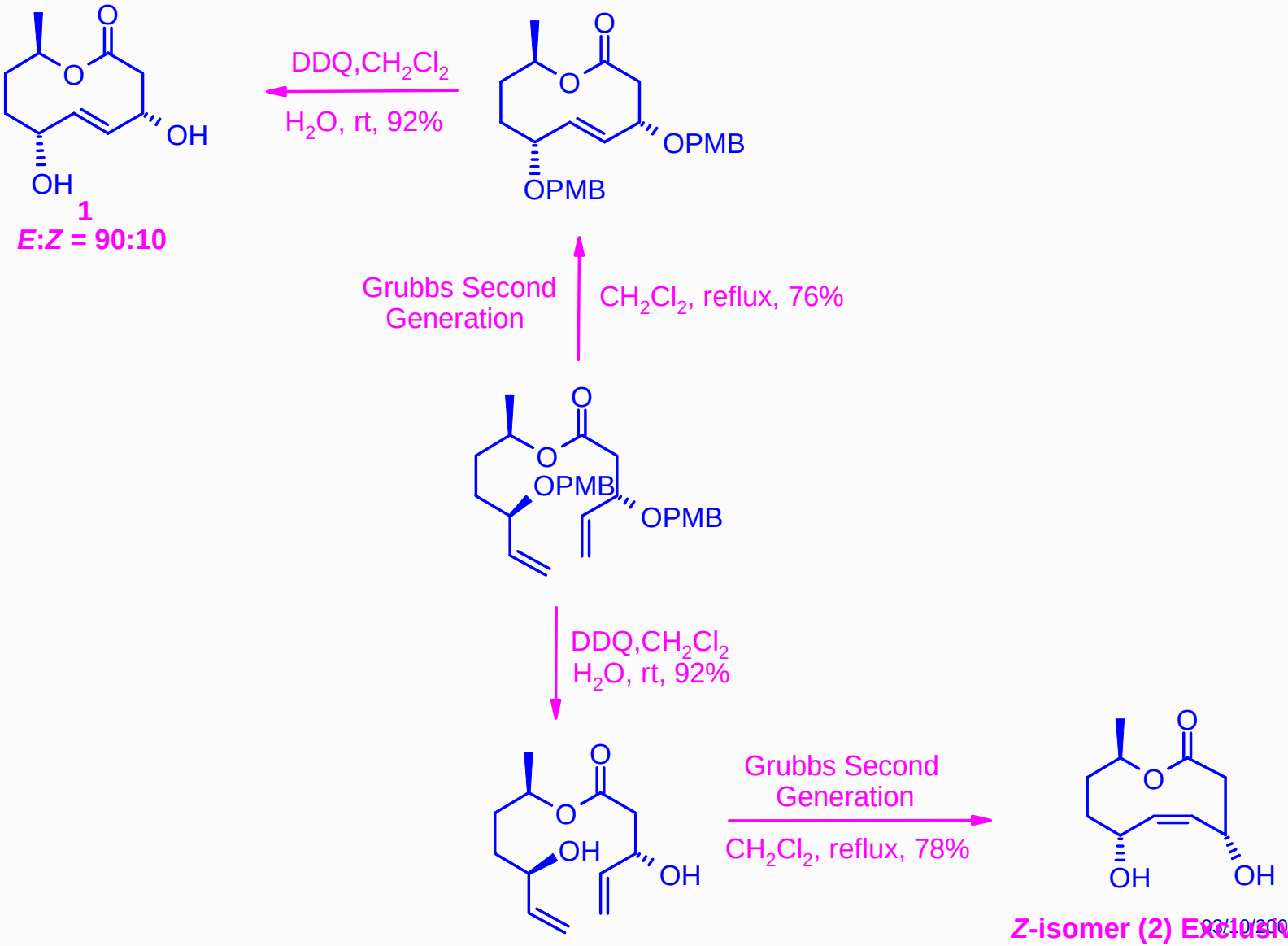
Rukachaisirikul, V.; Pramjit, S.; Pakawatachai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953-1955.

Probable Stereochemical Outcome





Synthesis of Nonenolide and its *Z*-Isomer



Retrosynthesis of Microcarpalide